REMARKS

Claims 50, 51, 53-63, 65, and 70-97 were pending in the application. Claims 50, 51, 53-63, 65, 70-73, 75, 79-89, 91, 92, and 95-97 have been cancelled without prejudice to presentation in future related applications. Claims 74, 78, 90, 93, and 94 have been amended for further grammatical clarity and to recite an active step of diagnosing colon, breast or prostate cancer in a patient. Claim 90 has been amended to clarify that the polynucleotide hybridizes to the complement of the recited nucleic acid and recite hybridization conditions. Support for the amendment to claim 90 can be found, for example, at paragraph [0085]. Unless otherwise indicated, paragraph numbering is based on Publication No. US 2007/0218071A1, which corresponds to the above-referenced application. No new matter has been added.

The specification has been amended at paragraphs [0082] and [0149] to delete references to hyperlinks. No new matter has been added.

Upon entry of this amendment, claims 74, 76-78, 90, 93, and 94 will be pending. Applicant respectfully requests reconsideration and allowance of claims 74, 76-78, 90, 93, and 94 in view of the above amendments and following remarks.

Interview Summary

Applicants thank the Examiner for the courtesy of a phone interview with Mr. Attwell on February 20, 2008. Applicants confirm the election of breast cancer and acknowledge that the claims are being examined on the basis of the nucleotide sequence set forth in SEQ ID NO:43.

Specification

The Office objected to the specification for containing an embedded hyperlink at paragraph [0149]. The specification at paragraph [0149] has been amended to delete the hyperlink. Accordingly, the Office is requested to withdraw the objection to the specification.

Oath/Declaration

The Office alleged that the oath or declaration was defective because non-initialed and/or non-dated alterations of the inventor, David W. Morris, have been made. Applicants disagree.

The declaration filed on November 15, 2004, does not contain any alterations and accordingly, is not defective. A copy of the declaration filed on November 15, 2004, is attached for the Office's convenience in reviewing this response.

Rejection under 35 U.S.C. §112, first paragraph

The Office rejected claims 61, 74-76, 78-81, 84-88, and 90-97 under 35 U.S.C. §112, first paragraph, for an alleged lack of written description. The Office alleged that:

> The claimed methods are inclusive of a genus of variants comprising addition, deletion, and/or substitution of VLDLR having 95% or 98% identity to SEQ ID NO:43 that could be hybridized. However, the instant specification fails to describe enough species of the polynucleotide, complement of VLDLR mRNA comprising or having 95% or 98% sequence identity to the polynucleotide of SEQ ID NO:43, which are detected and could be used for diagnosing breast cancer. It is also noted that "a nucleotide sequence" (claims 61, 90 etc.) and "a sequence" (claim 94 etc.) read on a as small as few nucleic acid residues and "a polynucleotide that hybridized to a nucleotide sequence of SEQ ID NO:43 (claim 90) reads on a fragment of SEQ ID NO:43. Thus, there is no showing that the inventor constructed an embodiment or performed a process that met all the limitations of the claims and determined that the invention would work for its intended purpose.

Claims 61, 75, 79-81, 84-88, 91, 92, 96, and 97 have been cancelled without prejudice to continued prosecution. Claim 74 has been amended to recite that the method for diagnosing colon, breast or prostate cancer in a patient includes comparing a level of VLDLR mRNA having a nucleotide sequence at least 95% identical to the sequence of SEQ ID NO:43 in a patient sample comprising colon, breast or prostate tissue to the level of the VLDLR mRNA in a normal control; and diagnosing colon, breast or prostate cancer in the patient based on an increase of at least 50% from the level of the VLDLR mRNA in the patient sample relative to the level in the normal control. Claim 90 has been amended to recite contacting a polynucleotide that hybridizes under highly stringent conditions to a nucleic acid having the nucleotide sequence of SEQ ID NO:43 with nucleic acids of a patient colon, breast or prostate sample under binding conditions

suitable to form a duplex, wherein hybridization is performed at 50°C to 60°C in 5 X SSC (9 mM saline /0.9 mM sodium citrate); and (b) comparing the amount of the duplex formed to the amount of duplex formed when the polynucleotide is contacted with nucleic acids of a non-cancerous colon, breast or prostate control, and c) diagnosing colon, breast or prostate cancer based on an increase of at least 50% of the amount of duplex formed upon contacting the polynucleotide with the nucleic acids of the patient sample compared to the amount of duplex formed upon contacting the polynucleotide and the nucleic acids of the non-cancerous control.

Applicants submit that independent claims 74 and 90 have written description sufficient to satisfy the MPEP, the Written Description Guidelines, and the relevant case law. An adequate description is one that describes the claimed invention in sufficient detail that one of ordinary skill in the art can reasonably conclude that the inventor had possession of the claimed invention. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555 (Fed. Cir. 1991). Possession may be shown in a variety of ways. For example, possession can be found where an Applicant presents drawings of the claimed invention (as in *Vas-Cath*) or structural chemical formulas. An Applicant may also describe distinguishing identifying characteristics. *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55 (1998); *Amgen, Inc. v. Chugai Pharm.*, 927 F.2d 1200 (Fed. Cir. 1991) (one may define a compound by "whatever characteristics sufficiently distinguish it").

With respect to the number of species disclosed, the Written Description Guidelines from the January 2001 *Federal Register* (at page 1106, emphasis added) state:

> Satisfactory disclosure of a "representative number" [of species] depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed.

Although neither the PTO nor the Federal Circuit has provided specific guidance on exactly how many species constitute a "representative number of species," Applicants respectfully assert that the nucleic acid of SEQ ID NO:43 is representative of the genus of sequences – i.e. nucleic acids having at least 95% sequence identity to the sequence of SEQ ID NO:43 that are diagnostic of breast cancer. The nucleic acid of claim 74 is defined structurally,

i.e., contains a highly similar nucleotide sequence. For example, each and every one of the species encompassed by the genus of claim 74 must include a sequence at least 95% identical to SEQ ID NO:43. Furthermore, the present specification describes variants and methods of making them (see, e.g., paragraphs [0129]-[0134]). Accordingly, Applicants have described the necessary common attributes of *all* of the sequences claimed.

The nucleic acids of claim 74 are also in accordance with Revision 1 of the Written Description Training Materials (March 25, 2008). See, Examples 10 and 11A. All of the species within the genus share a significant degree of partial structure (i.e., at least 95% of SEQ ID NO:43). Applicants note that the level of identity recited in the present claims is higher than that of Example 11A of the Written Description Training Materials (85%), thereby further decreasing any potential variation between species. With the aid of a computer, one of ordinary skill can easily and with 100% predictability envision every possible sequence that satisfies the criteria of the claimed genus. Thus, the specification describes 95% of the structure that defines the nucleic acids within the claimed genus.

Given Applicants' description in the specification, one of ordinary skill in the art would have no difficulty in envisioning all of the claimed species and would conclude that Applicants were in possession of those nucleic acids. Thus, in view of the specification and knowledge in the art, one of ordinary skill would have realized that the inventors provided a representative number of species within the genus of nucleic acid sequences having at least 95% identity to SEQ ID NO:43.

With respect to claim 90, Applicants submit that the disclosure of SEQ ID NO:43 combined with knowledge in the art regarding hybridization would put one in possession of the genus of nucleic acids that would hybridize under stringent conditions to the complement of SEQ ID NO:43. As noted in Example 6 of the Written Description Training Materials, hybridization under highly stringent conditions requires a high degree of structural complementarity, nucleic acids that hybridize to the recited sequence must share many nucleotides in common with the recited sequence. Thus, one of ordinary skill in the art would put one in possession of the genus

of nucleic acids that would hybridize under stringent conditions to the complement of SEQ ID NO:43.

The Office also alleged that "the art of record has not identified other variants of VLDLR or the gene expression products having at least 95% identity to SEQ ID NO:43 that is upregulated in the breast cancer cells or tissues and no teaching or suggestion in the record of the art on the mutation or substitution of the gene product with 95% or 98% identity to the DNA of SEQ ID NO:43 in the breast cancer development or cancer condition has been recorded."

The silence of the cited reference with respect to variants of VLDLR being upregulated in breast cancer fails to indicate that the present specification lacks written description. Rather, as discussed above, the specification provides sufficient written description for nucleic acids having at least 95% identity to SEQ ID NO:43 and hybridization to such nucleic acids as recited in claims 74, 76-78, 90, and 93-94.

Accordingly, the Office is requested to withdraw the rejection under 35 U.S.C. §112, first paragraph, for an alleged lack of written description.

The Office rejected claims 61, 74-76, 78-81, 84-88, and 90-97 under 35 U.S.C. §112, first paragraph, for an alleged lack of enablement. The Office asserted that "the specification teaches few variants of SEQ ID NO:43 with several nucleotide differences in C-terminal untranslated region, for example SEQ ID NO:47, 51, etc. may also be associated with cancer (see search result of SEQ ID NO:43 in SCORE), the specification does not teach other variants of SEQ ID NO:43 that contains [sic] an addition, deletion, or substitution at coding regions having at least 95% or 98% sequence identity to the SEQ ID NO:43 which are differentially expressed in the breast cancer condition."

Claims 61, 75, 79-81, 84-88, 91, 92, 96, and 97 have been cancelled without prejudice to continued prosecution. Claims 74 and 90 have been amended as discussed above. The specification indicates that SEQ ID NO:43 is a cancer associated sequence. One of ordinary skill in the art can readily determine if expression of a nucleic acid having the nucleotide sequence set forth in SEQ ID NO:43, or a nucleic acid having at least 95% identity to SEQ ID NO:43, is increased relative to that of a control breast, colon or prostate tissue sample as recited in claims

74, 76, 78, 93, and 94. One of ordinary skill in the art also can readily determine if the amount of duplex formed upon contacting a polynucleotide that hybridizes under highly stringent conditions to the complement of a nucleic acid having the nucleotide sequence set forth in SEQ ID NO:43 with a patient sample is increased relative to the amount of duplex formed by hybridization of such a polynucleotide to nucleic acid in a control non-cancer sample (see claim 90). The specification provides detailed guidance for detecting mRNA, e.g., at paragraphs [0176] and [0181] of the specification and for hybridization, e.g., at paragraphs [0085] and [0086] of the specification. One of ordinary skill in the art will appreciate that increased expression of VLDLR can be used to facilitate diagnosis of breast cancer.

The Office also asserted that in view of Martensen et al., one skilled in the art knows that not all VLDLR variants are involved in cancer or breast cancer condition or contribute to cancer development.

The silence of the cited reference with respect to variants of VLDLR being upregulated in breast cancer fails to indicate that the present specification lacks enablement. Rather, as discussed above, the specification provides detailed guidance for one of ordinary skill in the art to practice the methods of claims 74, 76-78, 90, and 93-94. Accordingly, the Office is requested to withdraw the rejection under §112, first paragraph, for an alleged lack of enablement.

Rejections under 35 U.S.C. §102

The Office rejected claims 61, 74-81, 84-90, and 93-97 under 35 U.S.C. §102(b) as allegedly being anticipated by Martensen et al. (Eur. J. Biochem. 248:583-591, 1997). The Office alleged that Martensen et al. disclose "a method which would be used for diagnosing a breast cancer by determining the levels of expression of VLDLR." The Office further alleged that the "phrase 'wherein an increase of at least 50%, 100%, 200% etc. from the levels of the mRNA in the breast patients sample relative to normal control' recited in the claims are not considered as an active method step."

Claims 75, 79-81, 84-89, 91, and 92 have been cancelled. Amended independent claims 61, 74, and 90 recite an active step of diagnosing cancer based on an increase in the expression

product. The Martensen et al. reference does not disclose that cancer can be diagnosed based on an increase of at least 50% between the level of the expression product in the individual's tissue sample and a control sample. Rather, the Martensen et al. reference discloses that breast carcinomas expressed predominantly a VLDLR variant lacking exon 16 as determined by RT-PCR. Accordingly, the Martensen et al. reference does not anticipate claims 61, 74, 76-78, 90, and 93-97. The Office is requested to withdraw the rejection under §102(b) over Martensen et al.

The Office rejected claims 61, 74-81, 84, 86-89, and 94-97 under 35 U.S.C. §102(a) or 102(e) as allegedly being anticipated by Hopkins et al. (U.S. Patent Publication No. 2002/0137077). The Office alleged that Hopkins et al. disclose that SEQ ID NO:5, which encodes VLDLR, is up-regulated two-fold and can be used for diagnosing cancer.

Claims 75, 79-81, 84, and 86-89 have been cancelled without prejudice. Amended independent claims 61 and 74 recite an active step of diagnosing cancer based on an increase in the expression product. The Hopkins reference does not disclose that a VLDLR expression product is up-regulated and can be used to diagnose cancer (e.g., breast cancer). Rather, the Hopkins et al. reference discloses that SEQ ID NO:5 is down-regulated two-fold or more in activated T cells. See paragraph [0047] of Hopkins et al. Accordingly, the Hopkins et al. reference does not anticipate the methods of claims 61, 74-81, 84, 86-89, and 94-97. The Office is requested to withdraw the rejection under 35 U.S.C. §102(a) or 102(e) over Hopkins et al.

Rejection under 35 U.S.C. §103

The Office rejected claims 90-93 under 35 U.S.C. §103 as allegedly being unpatentable over Hopkins et al. in view of Martensen et al. and Fodor et al. (U.S. Patent No. 5,872,928). Applicants disagree.

Claims 91 and 92 have been cancelled without prejudice. Amended claims 90 and 93 recite an active step of diagnosing cancer based on increased levels of the amount of duplex formed (claim 90) or an increase in the expression product (claim 93). As discussed above, the Hopkins et al. reference discloses that SEQ ID NO:5 is down-regulated two-fold or more in

activated T cells. The Martensen et al. reference discloses that breast carcinomas expressed predominantly a VLDLR variant lacking exon 16 as determined by RT-PCR. The Fodor et al. reference discloses methods for analyzing nucleic acids. The combination of cited references does not disclose that cancer can be diagnosed based on an increase of at least 50% in the amount of duplex formed as recited in claim 90 or between the level of the expression product in the individual's tissue sample and a control sample as recited in claim 93. Accordingly, the combination of cited references does not render claims 90 and 93 obvious and the Office is requested to withdraw the rejection under 35 U.S.C. §103.

CONCLUSION

It is believed that any pending objections and rejections have been addressed. However, the absence of a reply to a specific rejection, issue, or comment does not signify agreement with or concession of that rejection, issue, or comment. In addition, because the arguments made above may not be exhaustive, there may be reasons for patentability of any or all pending claims (or other claims) that have not been expressed. Finally, nothing in this paper should be construed as an intent to concede any issue with regard to any claim, except as specifically stated in this paper, and the amendment of any claim does not necessarily signify concession of unpatentability of the claim prior to its amendment.

Applicants submit that claims 74, 76-78, 90, 93, and 94 are in condition for allowance, which action is requested. Please apply the three-month Petition for Extension of Time fee and any other charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: September 30, 2008

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